Impact of obesity and diabetes on colorectal cancer in Saudi Arabia is associated with liver γ-glutamyl transferase abnormality

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Abstract. Colorectal cancer (CRC) is a leading global cause of death. In Saudi Arabia, it is the most common cancer among men and the third most common among women. Obesity, diabetes and CRC have become significant health concerns. The present study aimed to explore the connection between liver function markers, obesity and diabetes in patients with CRC. In addition to exploring whether the incidence of CRC had increased in Saudi Arabia. The present study conducted a retrospective chart review based on data from the Saudi Ministry of National Guard Hospitals. Clinical laboratory assays of patients with CRC with obesity and/or diabetes between 2015 and 2021 were analysed, and various factors were considered. This study found that CRC is more prevalent in overweight and obese individuals, primarily aged 50 years and older. Diabetes was more common in patients with CRC (61.76%) compared with non-diabetic individuals (38.24%). Additionally, the protein γ-glutamyl transferase might serve as a potential biomarker for CRC in overweight and obese patients. Notably, the age of CRC diagnosis in Saudi Arabian patients in the present study was lower than previously reported. The present study provided insight into the relationship between obesity, diabetes and liver function markers in Saudi Arabian patients with CRC. It also highlighted the increasing incidence of CRC in Saudi Arabia, emphasizing the need for further attention and research.

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Introduction

Colorectal cancer (CRC) is one of the most prevalent types of cancer worldwide, with a varying incidence from country to country. In the United States of America, it is the third most commonly diagnosed cancer in both men and women, while it is the most diagnosed cancer among men and the third most diagnosed cancer among women in Saudi Arabia, as of a 2018 report (1). The incidence of CRC is increasing in Saudi Arabia, with a median detection age of 55 years in women and 60 years in men (2). Despite being less common in Saudi Arabia compared with some other countries, CRC is the leading cause of cancer mortality among men and top five in women (3). This represents a significant health concern. The Saudi Ministry of Health aims to reduce the impact of CRC by introducing screening and diagnostic programs. CRC may occur infrequently due to genetic cancer syndromes or inflammatory bowel disorders. However, even if they don't meet the criteria for hereditary CRC, ~20% of all cases of this disorder are considered to have some degree of familial risk (4).

Certain risk factors, such as diet, smoking and obesity, are associated with some of the most common forms of cancer, including breast, gynaecological, liver and CRCs (5,6). Obesity is characterized by the accumulation of excess body fat, which leads to a higher risk of metabolic syndrome. The global obesity epidemic is a significant public health issue, and Saudi Arabia is one of the countries with the highest obesity rates, at 24% (7). As obesity becomes more prevalent, research into the link between excess weight and CRC has become more prominent. Based on multiple studies, obese patients with CRC tend to have shorter survival rates, as discussed previously (8,9)

Insulin resistance and hyperinsulinemia are significant contributors to CRC (10,11). Insulin resistance is a form of type 2 diabetes. Diabetes mellitus (DM) is a general term that encompasses a wide range of metabolic disorders, with

chronic hyperglycaemia being the most common. Type 2 diabetes affects 18.3% of the population in Saudi Arabia (12). Although various epidemiological studies have shown that the prevalence of CRC is higher among diabetic patients than non-diabetic individuals, some studies, particularly those investigating the risk of CRC, have considered type II diabetes as more prevalent and relevant (13,14).

The liver plays a vital role in metabolism by converting carbohydrates, fats, proteins and lipids into active forms that circulate in the blood (15). Additionally, it functions to detoxify harmful substances and produce essential enzymes for cell growth and energy expenditure (16). Abnormalities in liver function can result in various diseases including CRC (17) and cirrhosis (18). A recent UK biobank analysis suggests that higher levels of alanine transaminase (ALT), aspartate transferase (AST), total bilirubin (TBIL), γ-glutamyl transferase (GGT), prothrombin time (PT) and albumin (ALB) may be associated with lower risk for CRC (19). Studies have also found associations between markers of liver function such as ALT bilirubin and albumin with chronic illnesses including CRC as well as increased toxicity among patients diagnosed with this type of cancer (19-21).

The purpose of the present study was to provide an updated report on the rates of obesity and diabetes among CRC patients in Saudi Arabia and to investigate how these conditions were associated with the elevation of liver metabolite markers such as ALT, AST, bilirubin, GGT, ALB and lactate dehydrogenase (LDH). By doing so, the study aims to provide further evidence regarding the role played by obesity and diabetes as widespread factors in Saudi Arabia in the progression of CRC.

Patients and methods

Patient data. The present study was a retrospective chart review that utilized medical records from the Saudi Ministry of National Guards Hospital and Health Affairs, which is a tertiary hospital located in Riyadh, Saudi Arabia. The study was approved by the King Abdullah International Medical Research Center Institutional Review Board (IRB), Ministry of National Guard-Health Affairs (approval no. NRC22R/144/03). The IRB approved the waiver of informed consent when using medical records since research involves no more than minimal risk to the subjects.

The selection criteria included all medical records of patients who were diagnosed with CRC between January 2015 and December 2019 and met the inclusion criteria, which was a confirmed CRC diagnosis. The present study employed a non-probability consecutive sampling technique to select the patients, which means all conveniently available populations were included. The confounding variables were addressed through matching. The assessment of each patient included their age, sex, body mass index (BMI), complete blood cell count, haematocrit, haemoglobin, platelet count, liver profile (TBIL, ALB, GGT, direct bilirubin, AST, LDH, ALT and PT), kidney profile (creatinine, estimated glomerular filtration rate) and diabetes status. Exclusion criteria included patients with incomplete clinical records or missing treatment information. The study included 147 women and 172 men. The BMI was calculated according to standard scale: BMI ≥30 was obese, ≥25 was overweight, ≥18.5 was normal and <18.5 kg/m^2 was underweight as mentioned previously (22).

Statistical analysis. The present study used Epi Info 7.2.5 software (trademark of CDC, USA) for statistical analysis of the data, a tool designed for epidemiological statistics in public health practice. To assess significance, a one-tailed P-value and employed Pearson's χ^2 test was used. P<0.05 was considered to indicate a statistically significant difference. Significance calculations were based on a confidence interval of 95%. In the tables, (Row%) refers to row percentage which represents the proportion or percentage of a specific row's value in relation to the total of that row. Similarly, (Col%) refers to column percentage which represents the proportion or percentage of a specific column's value in relation to the total of that column. The survival data was created by OncoLnc data portal (http://www.oncolnc.org/), which links survival data from The Cancer Genome Atlas (TCGA) to mRNA, microRNA and long non-coding RNA expression levels. The data was downloaded on July 1, 2023 (23).

Results

Age groups and CRC prevalence. The present study reviewed 319 patients when investigating the prevalence of CRC among different age groups between January 2015 and December 2019 (Table I). The participants were divided into four categories: i) Under 30 years; ii) 30-49 years; iii) 50-59 years; and iv) ≥60 years. Reviewing CRC frequencies showed that there were only 3 individuals under the age of 30, while there were 70 between the ages of 30 and 49 years, 115 between the ages of 50 and 59 years, and 131 ≥60 years (Table I). The groups 50-59 years and ≥60 years had higher patient percentages, at 36.05 and 41.07%, respectively. The other two groups of 30-49 years and <30 years had less members, at 21.94 and 0.94%, respectively. The age range for males was 24-95 years old, while that for females was 36-87 years old. The median age for the entire sample was 57 years, while the median age was 58 years for men and 57 years for women. Applying the null hypothesis revealed that age classification had significant P-value (P<0.01) in comparison to the healthy control (Table I).

Sex. In order to gain a deeper understanding of the prevalence of CRC, an analysis of sex contributions to the incidence of CRC was conducted. The participants were divided into two categories based on sex: Male and female. The findings showed a sex disparity in the incidence rates of CRC across age demographics. Specifically, among female patients, 55 (37.41%) were ≥60 years, 57 (38.78%) were 50-59 years, 35 (23.81%) were 30-49 years and 0 (0.0%) were <30 years. Meanwhile, among male patients, 76 (44.19%) were ≥60, 58 (33.72%) were 50-59 years, 35 (20.35%) were 30-49 years and 3 (1.74%) were <30 years (Table II).

This analysis revealed that males had a higher percentage of CRC incidence compared with females in two age groups: ≥60 and <30 years. Specifically, the incidence rate of CRC among males was 16% higher for those ≥60 years and 100% for those <30 years when compared with females of the same age groups. These results may be of value in developing sex-specific strategies for the prevention and treatment of CRC.

Table I. Prevalence of colorectal cancer in correlation with age.

Age in years	n (%)	One-tailed P-value
<30	3 (0.94)	0.0001
30-49	70 (21.94)	0.0034
50-59	115 (36.05)	0.0067
≥60	131 (41.07)	0.0082
Total	319 (100.00)	-

Two-tailed P-value was calculated and significance was considered at P≤0.01.

Table II. Investigating the prevalence of colorectal cancer based on sex.

	Age in years				
Sex	<30	30-49	50-59	≥60`	Total
Female	0	35	57	55	147
Row%	0.00	23.81	38.78	37.41	100.00
Col%	0.00	50.00	49.57	41.98	46.08
Male	3	35	58	76	172
Row%	1.74	20.35	33.72	44.19	100.00
Col%	100.00	50.00	50.43	58.02	53.92
Total	3	70	115	131	319
Row%	0.94	21.94	36.05	41.07	100.00
Col%	100.00	100.00	100.00	100.00	100.00

(Row%) refers to row percentage, while (Col%) refers to column percentage.

BMI. The results presented in Table III present the investigation into the relationship between BMI measurements and their association with CRC. Patients were classified into normal, underweight, overweight or obese categories based on BMI. Frequency and percentage data were obtained for each group by sex. The results reveal that the majority of patients with CRC 185 (57.9%) are overweight, which includes obese patients. Notably, participants with a normal BMI had a higher occurrence rate of CRC 112 (35.11%) compared with those with an underweight BMI category 22 (6.90%). This emphasizes the significance of maintaining lower BMI even if less than normal healthy weight levels when it comes to preventing and managing this type of cancer effectively. These numbers failed to confirm association statistically, as χ^2=5.38 and P=0.145.

Obesity and diabetes. The study investigated the link between obesity-related complications and diabetes incidence in 319 participants with CRC. The results, presented in Table IV, showed that out of a total of 147 women and 172 men, only 63 female patients (42.86%) did not have diabetes while the rest did; similarly, for males, only 59 (34.30%) did not have diabetes compared with 113 (65.70%) males who did. Measurement of risk ratio, risk differences and odd ratio turn-out to be 1.25, 8.55 and 1.44, respectively, at 95% confidence interval. The positive risk and odd ratio in these findings strongly suggest an association between CRC and diabetes among both sexes (P=0.05). Although more research is required to determine precisely how this connection occurs, these results indicate that people with type II Diabetes are at greater risk for developing CRC compared with those without it due to their condition caused by excessive body weight which can lead them into a higher rate of health problems associated with overweight or obese individuals.

Obesity and liver disease. The present study examined liver metabolite abnormalities in patients with CRC who were overweight or obese and diabetic to investigate the association between excess weight, diabetes and liver function markers. The objective was to establish a possible link between these factors. The results revealed that 106 (33.23%) of obese patients with CRC had significantly elevated levels of GGT enzyme (P=0.026; Table V). However, most overweight or obese patients with CRC showed normal levels of other indicators including ALT, LDH, AST, ALB and TBIL (Tables SI-SV). Improving our understanding of how obesity and diabetes affect the liver can be beneficial for managing related health issues among CRC sufferers.

Obesity and GGT. In 197 diabetic patients with CRC, the present study examined a link between overweight/or obesity and GGT levels when compared to 122 non-diabetic patients with CRC in Table VI. The subjects were split into four groups based on their GGT and whether they had diabetes. The first group was made up of 33 people (27.05%), all of whom had a normal BMI and did not have diabetes. The second group was made up of 45 individuals (22.84%) with diabetes and a normal BMI. The third group had 38 patients (31.15%), none of whom had diabetes but whose BMI was abnormally high. The fourth group was made up of 16 patients (13%), all of whom had diabetes and an abnormal BMI. The result of this categorization (data not shown) show that there were more people with diabetes in the normal BMI group 45 (57.69%) than people without diabetes 33 (42.31%) in the normal group. In the group of people with an abnormal BMI, there were more people with diabetes 68 (64.15%) than people without diabetes 38 (35.85%) (P=0.04; Table VI).

Diabetes and GGT. The present study subsequently evaluated patients with CRC exhibiting GGT abnormalities and further classified these patients based on their diabetic status, as shown in Table VII. Out of the total 183 patients, 44 (55.70%) of the women were diabetic and 35 (44.30%) were non-diabetic. By contrast, 71 (68.27%) of the men were diabetic and 33 (31.73%) were non-diabetic. Notably, the risk ratio, risk differences and odds ratio increased to 1.39, 12.57 and 1.71, respectively. These changes were significant (P=0.05).

GGT level in public database. The present study analysed the levels of GGT6 in colon adenocarcinoma, using TCGA database through Oncolnc tool. The OncoLnc is a data portal that explore correlations between survival data and gene expression from TCGA. Based on the data, the present study reported a significant correlation (P=0.0469) between the reduction in GGT6 and poor prognosis, as depicted in Fig. 1.

Table III. Association between obesity (body mass index) and sex of colorectal cancer.

	BMI status				
Sex	Normal	Obese	Overweight	Underweight	Total
Female, n (%)	45 (30.61)	55 (37.41)	36 (24.49)	11 (7.48)	147 (100.00)
Male, n (%)	67 (38.95)	45 (26.16)	49 (28.49)	11 (6.40)	172 (100.00)
Total, n (%)	112 (35.11)	100 (31.35)	85 (26.65)	22 (6.90)	319 (100.00)

Not significant since χ^2=5.38 and P=0.145.

Table IV. Association between colorectal cancer with diabetes among both male and female populations.

	Diabetes (yes/no)		
Sex	No	Yes	Total
Female, n (%)	63 (42.86)	84 (57.14)	147 (100.00)
Male, n (%)	59 (34.30)	113 (65.70)	172 (100.00)
Total, n (%)	122 (38.24)	197 (61.76)	319 (100.00)

Table is not significant since χ^2=2.45 and P>0.05.

Table V. Association between high body mass index and liver function metabolites in patients with colorectal cancer.

BMI vs. liver GGT	n (%)
Abnormal liver GGT	106 (33.23)
Not overweight with abnormal GGT	135 (42.32)
Normal liver GGT	78 (24.45)
Total	319 (100.00)

Table is significant for abnormal GGT since χ^2=3.1 and P=0.026. GGT, γ-glutamyl transferase.

Table VI. Association between body mass index, GGT levels and diabetic status in patients with colorectal cancer.

	Diabetes (yes/no)		
BMI vs. liver GGT	No	Yes	Total
Abnormal, n (%)	38 (35.85)	68 (64.15)	106 (100.00)
NA, n (%)	51 (37.78)	84 (62.22)	135 (100.00)
Normal, n (%)	33 (42.31)	45 (57.69)	78 (100.00)
Total, n (%)	122 (38.24)	197 (61.76)	319 (100.00)

NA is not applicable, which refers to underweight BMI. Table is significant since χ^2=3.25 and P=0.04.

Table VII. Association between abnormal GGT levels and diabetic status then weighted by sex in patients with colorectal cancer.

	Diabetes (yes/no)		
Sex	No	Yes	Total
Female, n (%)	35 (44.30)	44 (55.70)	79 (100.00)
Male, n (%)	33 (31.73)	71 (68.27)	104 (100.00)
Total, n (%)	68 (37.16)	115 (62.84)	183 (100.00)

Table is significant since χ^2=3 and P=0.05.

Discussion

CRC ranks as the third most prevalent type of cancer worldwide and stands as the second leading cause of death from cancer (1). Unhealthy lifestyle habits, such as high BMI, smoking, alcohol consumption and poor diet have been associated with CRC onset (13). Notably, several studies also link hyperglycaemia to a higher incidence of CRC (24). Another study based on UK biobank data highlights that liver enzymes play an essential role in CRC progression (19). The present research revealed that individuals diagnosed with CRC were more likely to be diabetic or overweight. Furthermore, the present study suggested that the GGT enzyme could serve as a valuable predictive marker for detecting early-stage colon cancers.

A previous study conducted by The International Agency for Research on Cancer stated that cancer incidence and prevalence generally increase with age, particularly after the age of 50 (25). Additionally, it has been established that there exists an association between sex and CRC incidence, wherein men are at higher risk for developing CRC compared with women. The same study revealed that ~23 out of every 100,000 men have this condition in comparison to only ~16 cases per 100,000 women (25). Most participants in the present research were aged >50 years, which further supports the link between patient age and CRC progression. The finding also suggests sex differences play a role in contributing towards the development of CRC as more males had this disease compared with females.

Based on the present results, it appeared that individuals aged ≥60 years had a significantly higher incidence rate of CRC (41.07%), whereas those aged <30 years have an incidence rate of only 0.94%. A two-tailed test conducted on the data revealed a significant difference between the two groups, with P=0.001.

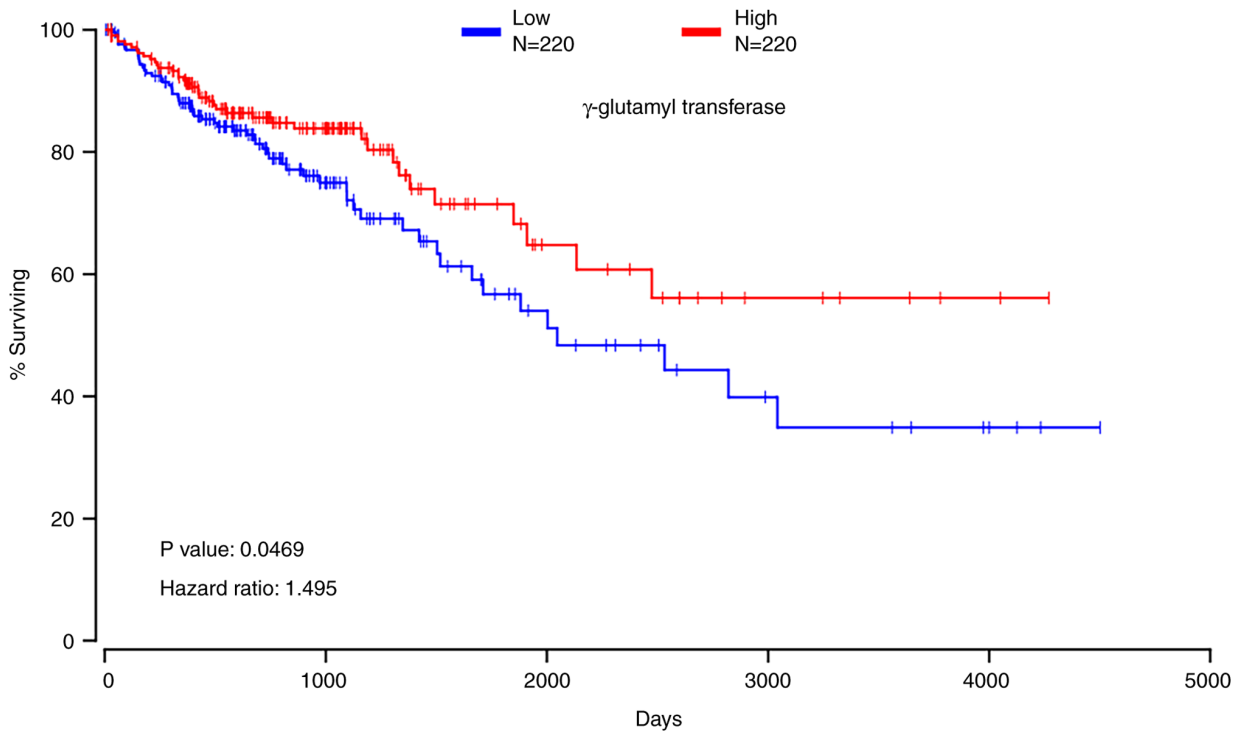

Figure 1. Survival percentage of patients with colorectal cancer in association with γ-glutamyl transferase using The Cancer Atlas Genome database.

These results highlight the crucial role of age as a predictive factor in preventing and treating CRC. Consequently, there is a need to implement age-specific screening measures as a critical preventive measure against this illness.

The analysis conducted on the incidence of CRC in males and females shows that males may be at a higher risk of developing this malignancy than females. The data suggested that, despite advancements in cancer prevention and diagnosis, males continue to have a higher incidence rate, indicating the urgency for further research on colon cancer prevention. These findings underscore the need for more focused and concerted efforts on colon cancer prevention and research among males. Additionally, more extensive research is required to better understand the underlying mechanisms of this malignancy. Such understanding can help in developing targeted and effective intervention strategies to curb the rise in the incidence of CRC, especially among males, and mitigate the burden of this disease on population health.

The connection between obesity and CRC is well established, with the accumulation of visceral adipose tissue (VAT) serving as a hallmark for this condition (26,27). Lipoid tissues are responsible for secreting hormones such as leptin, adiponectin and resistin, which can have an impact on insulin resistance (28,29). The build-up of VAT in the body creates a state of persistent low-grade systemic inflammation that exacerbates insulin resistance (30,31). The accumulation of VAT can cause persistent low-grade inflammation that worsens insulin resistance and promotes tumour growth within the microenvironment (32). The measures used to determine obesity include both BMI and waist circumference. The present study relied solely on BMI to evaluate obesity, which provided further evidence for obesity being a significant risk factor for CRC development as previously reported (33).

Diabetes is associated with several types of cancer, including colon, liver, pancreas, endometrial and breast cancer (34). Both diabetes and obesity lead to insulin resistance and hyperinsulinemia in patients triggering cell signalling pathways that cause tumorigenesis (35). The insulin-like growth factor 1 signalling pathway promotes cell proliferation while inhibiting apoptosis in CRC cells (36). The present study showed a prevalence of ≥60% for obesity and diabetes among patients with CRC; hence it is imperative to manage these conditions to prevent CRC.

In a recent UK biobank data analysis, it was found that higher levels of ALT, AST, TBIL, GGT, PT and ALB are associated with lower risk for CRC (19). Furthermore, previous studies have indicated a correlation between liver function markers such as ALT, bilirubin and ALB with chronic diseases, including CRC (19-21). To better understand the impact of the GGT enzyme in CRC, the current study examined the levels of GGT6 in colon adenocarcinoma from TCGA database. The findings showed a significant association (P=0.0469) between the downregulation of GGT6 and poor prognosis. The present study in Saudi Arabia supports previous reports that suggest using abnormal liver enzymes as markers in patients with CRC. The present study revealed that obese individuals had elevated levels of GGT, which confirmed and complemented previous research (37-39). Additionally, the current study revealed that diabetic individuals with CRC also had high levels of GGT, indicating its potential use as an indicator marker for overweight or diabetic patients with CRC.

The present study revealed a low familial prevalence of CRC with only 0.62% (1 patient) of participants reporting a family history. This may suggest a lower genetic predisposition in our sample, or possibly underreporting. However, in line with the majority of CRC cases being sporadic, 49.69%

(80 patients) of the study participants had no family history of the disease, emphasizing the significance of lifestyle factors and acquired genetic mutations in CRC development.

The management strategies for GGT involve several aspects. Monitoring GGT levels can help assess liver function and detect any liver damage or disease. Additionally, GGT levels can be used as a biomarker to evaluate the effectiveness of treatment and predict outcomes in patients with CRC with hepatic metastases (40). In the clinical management of CRC, patient-reported outcomes (PROs) play a crucial role. Self-reported symptoms, including those related to liver function, can guide the management of patients with CRC. Incorporating PROs into clinical trials and routine practice helps assess treatment efficacy and measure health-related quality of life (41).

It is important to note that GGT is not a direct treatment target in CRC management. Instead, it serves as an indicator of liver function and can provide valuable information for healthcare providers in monitoring and managing patients with CRC. The specific management strategies for GGT in CRC may vary depending on individual patient characteristics and the overall treatment plan. Therefore, it is essential for healthcare providers to interpret GGT test results in conjunction with other clinical information and tailor management strategies accordingly.

In summary, the current study highlighted the critical role of obesity and diabetes as major risk factors for the development of CRC in Saudi Arabia and potentially across the Arab States of the Gulf region. It is important to recognize the limitations of generalizing these findings to other populations. Conducting additional research with larger and more diverse cohorts would be valuable in confirming the observed associations and examining potential variations across populations. These conditions harm the colonic epithelium, leading to an increase in tumour formation that can metastasize and result in cancer-related deaths if left untreated. Additionally, we recommend further research to investigate the mechanisms connecting obesity, diabetes and CRC development, which would contribute to the existing knowledge in the field. Moreover, the present research draws attention to the growing incidence of CRC and proposes the need for preventive measures to curb its rise. Our research provides valuable insights into CRC prevalence, associated factors and the potential link between CRC and liver function enzymes in Saudi Arabia. This enhances our understanding of this significant health issue.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AMAlm, RHA, NFB and HHA collected data and organized it. GA, JAA, AMAlj and BMA analysed data. GA validated the data. BMA and GA supervised the project and wrote manuscript. BMA obtained resources. GA and BMA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of The Ministry of National Guard-Health Affairs approved this project (approval no. NRC22R/144/03).

Patient consent for publication

This work involves searching and analysing a hospital database, and the Institutional Review Board has waived the requirement for patient consent since no patients' identifiable information will be disclosed, and all data were coded and delinked.

Competing interests

The authors declare that they have no competing interests.

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